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Review Articles

Pediatric gliomas immunity challenges and immunotherapy advances

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Highlights

- Pediatric gliomas exhibit increased heterogeneity and distinct immune microenvironment.
- Immune microenvironment interactions influence tumor progression and response to treatment.

- Pediatric gliomas are classified as immune “cold” with an immunosuppressive microenvironment.
- Immunotherapeutic approaches enhance tumor immunogenicity and target immunosuppressive cells.

Abstract

Pediatric gliomas, the most frequent brain tumors in children, are characterized by heterogeneity and a unique tumor immune microenvironment. They are categorized into different subtypes, including low-grade gliomas like pilocytic astrocytomas and high-grade gliomas such as diffuse midline gliomas and diffuse intrinsic pontine gliomas, each exhibiting distinct immunological profiles. The tumor immune microenvironment in pediatric gliomas is shaped by cellular and non-cellular components, including immune cells, cytokines, and the extracellular matrix, involved in tumor progression, immune evasion, and response to therapy. While pediatric low-grade gliomas often display an immunosuppressed microenvironment, high-grade gliomas are characterized by complex immune infiltrates and intricate immunosuppressive mechanisms. The blood-brain barrier further obscures immune cell recruitment and therapeutic delivery. Despite advances in understanding adult gliomas, the immunobiology of pediatric tumors is poorly investigated, with limited data on the interactions between glioma cells and immune populations such as T and natural killer cells, as well as tumor-associated macrophages. Herein, we provide an update of the current knowledge on tumor immune microenvironment interactions in pediatric gliomas, highlighting the immunosuppressive mechanisms and emerging immunotherapeutic strategies aiming at overcoming these barriers to improve clinical outcomes for affected children.

Introduction

Pediatric brain tumors (PBT) represent the most common solid tumors and the primary cause of cancer-related deaths in children [1]. They are highly heterogeneous tumors with distinct genetic mutations, epigenetic profiles, and unique tumor immune microenvironments (TIME) [[2], [3], [4]]. Their prognosis remains poor, despite the significant advances in research and therapeutic approaches, particularly for high-grade gliomas (HGG) and medulloblastomas (MB), which exhibit aggressive behavior and high recurrence rates [5,6]. The immunobiology of PBTs is currently under extensive investigation aiming to decipher the processes that brain tumors use to interact with the immune system. The composition of the tumor microenvironment (TME) exerts a critical role in influencing immune responses to tumors, affecting tumor growth, metastasis and response to therapy [[7], [8], [9]]. However, there is a significant gap in knowledge about the immunological characteristics of PBTs since most studies are focused on adult gliomas [10]. Understanding the unique interplay of tumor cells with the immune system in PBTs is essential for developing effective therapies that improve patient outcomes and enable

personalized treatment strategies.

PBTs, based on the WHO classification, are grouped into pediatric low-grade gliomas and glioneuronal tumors (pLGG/GNTs), pediatric-type diffuse high-grade gliomas, embryonal, ependymal, and mesenchymal tumors [11]. pLGG/GNTs represent 30% of PBTs and are subcategorized into many subtypes according to their histology, biological characteristics, and immune infiltration. The major subtypes include pediatric-type diffuse low-grade gliomas, circumscribed astrocytic gliomas, glioneuronal and neuronal tumors. Each subtype possesses a distinct immunological profile, which, in turn, may influence the therapeutic strategies [12]. Even though pLGG is characterized by high myeloid cell infiltration and increased levels of cytotoxic $CD8^+$ T cells in specific subtypes, such as pilocytic astrocytoma (PA) [13], the high percentages of immunosuppressive tumor-associated macrophages ($CD163^+$TAM) indicate the presence of immune escape mechanisms [14]. Moreover, the TIME in pLGG is shaped by specific genetic alterations, such as mutations in the mitogen-activated protein kinase (MAPK) pathway [15]. High-grade gliomas (HGGs) in children, less common than pLGG, are highly aggressive with poor prognosis [16]. The subcategories of pHGG include diffuse midline glioma-H3K27-altered (DMG), diffuse hemispheric glioma, H3 G34-mutant, diffuse pHGG-H3-wildtype, IDH-wildtype (pHGG H3/IDH WT) and infant-type hemispheric glioma. DMG and more specifically, diffuse intrinsic pontine glioma (DIPG), located in the brainstem, often demonstrates a complex immune infiltration, even though previously have been considered as “immune cold tumors” [17]. pHGGs display heterogeneous TIME, characterized by variable expression of immune negative checkpoint molecules. In DMG, programmed death-ligand 1 (PD-L1) expressions correlated with a worse prognosis, whereas immune evasion via T cell immunoglobulin and mucin-domain containing-3 (TIM3) expression has been detected in children with diffuse hemispheric glioma, H3 G34-mutant glioma [18]. This heterogeneity in immune checkpoint expression highlights the complexity of the immune landscape in pHGG. Moreover, infiltrating NK cells have been observed in hemispheric pHGG compared to DMG [19]. Therefore, the presence and the density of activating immune cells within these tumors may indicate the immune surveillance of the tumor. However, the exact interplay between the tumor and these immune cells is not fully understood.

Ependymomas (EPN) are classified into different subtypes, each having a unique immune microenvironment. For example, posterior fossa ependymoma group A (PFA) has certain myeloid-derived subsets, like hypoxia myeloid-derived suppressor (MDSC) cells, which promote an immunosuppressive environment with poor T cell tumor infiltration [20]. On the other hand, MB (embryonal) and atypical teratoid/rhabdoid tumors have different immune characteristics [21,22]. MBs are characterized by sparse infiltration of $CD8^+$ T cells [23], whereas atypical teratoid/rhabdoid (AT/RT) tumors are marked by a more pronounced immune response, having higher $CD8^+$ T cells and eosinophils [24]. Changes in the immune microenvironment of these brain tumor subtypes affect their treatment responsiveness and clinical outcomes.

This review focuses on the composition of TIME in pediatric gliomas, highlighting the presence of activating and immunosuppressive immune cells. The mechanisms that these tumors have developed in order to escape immune surveillance and current immunotherapeutic approaches that may be applied to these patients are also explored.

Section snippets

Tumor microenvironment and immunogenicity in pediatric gliomas

The diversity and complexity of TME exerts a significant role in tumor growth and invasion since the immune microenvironment in pediatric gliomas exhibits unique characteristics, mainly attributed to the way immune responses are physiologically triggered in the brain [25,26]. In more detail, the Central Nervous System (CNS) is protected by a central element of this environment, the blood-brain barrier (BBB), which serves as a protective structure that controls the exchange of molecules between …

TIME and interactions in pediatric gliomas

The TIME is composed of different immune cell types from both innate and adaptive immunity, including B cells, T cells, TAMs, natural killer (NK) cells and eosinophils (Fig. 1, Table 1). …

Mechanisms evading immune surveillance in pediatric gliomas

In the era of cancer immunotherapy, the need for an in-depth understanding of TME and immune cells is indisputable in identifying the mechanisms of resistance to available immunotherapeutic modalities and predicting which patients would respond better to them. In general, glial-derived neoplasms, including those encountered in pediatric and young adult populations, such as DMG, are considered immunologically "cold, " showcasing limited infiltration by myeloid and lymphocytic origin cells. This …

Immunotherapeutic approaches

In line with the trend observed in a variety of solid and hematologic malignancies, where enhancing the immune system to eradicate tumor cells has become a cornerstone of therapeutic strategies, immunotherapy protocols have emerged as a promising treatment modality for pediatric gliomas. While the immunologically “cold” microenvironment of these tumors substantially limits the effectiveness of the classic ICIs regimens, numerous completed or ongoing clinical trials have evaluated the potential …

Future directions and conclusions

Immunotherapy is gaining ground for treating pediatric gliomas due to low mutational burden, immunosuppressive TIME, and the BBB that characterize them. Current immunotherapeutic approaches for PBTs include monoclonal antibodies, active immunization, and adoptive cellular therapy [157]. Therapeutic strategies modulating the TIME by targeting the infiltrating immunosuppressive cells, such as MDSCs, TAM and Treg, within TME might be a promising therapeutic intervention in order to enhance the …

CRediT authorship contribution statement

Eleni-Kyriaki Vetsika: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Maria A. Katsianou:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Panagiotis Sarantis:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Investigation, Formal analysis. **Kostas Palamaris:** Writing – review & editing, Writing – original …

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